DOI:10.1111/j.1365-2125.2005.02467.x

Fluvoxamine impairs single-dose caffeine clearance without altering caffeine pharmacodynamics

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Received
21 October 2004
Accepted
25 April 2005

Background
Coadministration of fluvoxamine impairs the clearance of caffeine and prolongs its elimination half-life, which is attributable to inhibition of CYP1A2 by fluvoxamine. The clinical importance of this interaction is not established.

Aim
To evaluate the effects of fluvoxamine on the kinetics and dynamics of single doses of caffeine.

Methods
Seven healthy subjects received single 250 mg doses of caffeine (or matching placebo) together with fluvoxamine (four doses of 100 mg over 2 days) or with matching placebo in a double-blind, four-way crossover study. For 24 h after caffeine or placebo administration, plasma caffeine and fluvoxamine concentrations were determined. Psychomotor performance, sedation, and electroencephalographic (EEG) 'beta' frequency activity were also assessed.

Results
Fluvoxamine significantly reduced apparent oral clearance of caffeine (105 *vs.* 9.1 mL min^{-1}, $P < 0.01$; mean difference: 95.7 mL min^{-1}, 95% CI: 54.9–135.6), and prolonged its elimination half-life (4.9 *vs.* 56 h, $P < 0.01$; mean difference: 51 h, 95% CI: 26–76). Caffeine produced CNS-stimulating effects compared with placebo. However, psychomotor performance, alertness, or EEG effects attributable to caffeine were not augmented by coadministration of fluvoxamine.

Conclusions
Fluvoxamine greatly impaired caffeine clearance, but without detectable changes in caffeine pharmacodynamics. However, this study does not rule out possible adverse effects due to extensive accumulation of caffeine with daily ingestion in fluvoxamine-treated individuals.

Introduction

Polypharmacy is widespread in clinical practice, and considerable attention has recently focused on pharmacokinetic drug interactions. A number of high profile cases of hazardous drug interactions, such as the terfenadine–ketoconazole interaction [1–3], have led to drug withdrawal. However, such examples are not common. Many statistically significant drug interactions

have been documented in controlled pharmacokinetic studies, but these may not necessarily be hazardous or even clinically detectable [4].

Fluvoxamine is a selective serotonin reuptake inhibitor indicated for the treatment of obsessive-compulsive disorder and major depressive disorder [5, 6]. It is also a potent inhibitor of human CYP1A2, both *in vivo* and *in vitro* [7–10]. Fluvoxamine inhibits the clearance of theophylline [11], a CYP1A2 substrate, and product labelling information for fluvoxamine suggests that clinicians decrease the dosage of theophylline by one-third when given together with fluvoxamine. Coadministration of fluvoxamine with caffeine, another CYP1A2 substrate, also results in impairment of caffeine metabolism and elevated plasma caffeine concentrations [8, 12]. Based upon such findings, some authors have advised clinicians to encourage caffeine restriction in patients on fluvoxamine therapy [13]. Despite such advice, the clinical importance of a caffeine–fluvoxamine interaction still remains to be demonstrated.

Caffeine is a CNS stimulant widely and frequently consumed in foods and beverages. To evaluate whether the clinical response to caffeine is altered by fluvoxamine coadministration, we assessed the effects of fluvoxamine on the pharmacokinetics and pharmacodynamics of caffeine in healthy subjects. We also utilized *in vitro* inhibition data for fluvoxamine and caffeine to determine whether the *in vitro* findings are predictive of the degree of inhibition of caffeine clearance by fluvoxamine *in vivo*.

Methods

Study design

The protocol and consent forms were reviewed and approved by the Human Investigation Review Committee serving Tufts University School of Medicine and Tufts-New England Medical Center. Seven subjects (six men, one woman, average age 50 years, average weight 82 kg) completed the study after giving informed consent. Three additional subjects failed to complete all four trials due to administrative reasons. All subjects were active ambulatory adults with no evidence of disease and taking no other medications. All subjects were nonsmokers based upon self-reports. Four of the participants were regular users of caffeine in the form of coffee or other caffeine-containing beverages. All subjects were asked to abstain from all caffeine-containing foods and beverages for 24 h prior to each study trial.

The study had a randomized, four-way crossover design, with at least 7 days elapsing between treatments. Medications were identically packaged in opaque capsules, and administered orally on a double-blind basis. The four treatment conditions were as follows:

Treatment A: Placebo to match fluvoxamine (LUVOX®, Solvay, Marietta, GA, USA), plus placebo to match caffeine

Treatment B: Placebo to match fluvoxamine, plus caffeine, 250 mg

Treatment C: Fluvoxamine, four doses of 100 mg each, plus placebo to match caffeine

Treatment D: Fluvoxamine, four doses of 100 mg each, plus caffeine, 250 mg.

The dosage regimen for fluvoxamine is based upon the literature from clinical trials and the usually prescribed dosages [5, 6, 14]. Cotreatment with fluvoxamine, 100 mg (or placebo), was as follows: the first dose was at 08.00 h on the morning prior to the trial, the second dose at 16.00 h on the afternoon prior to the trial, the third dose at 07.30 h on the day of caffeine or placebo administration, and the fourth dose at 17.00 h on the same day. The first, third, and fourth doses of fluvoxamine (or placebo) were administered under the supervision of the study personnel. The second dose was provided to subjects to be taken on an outpatient basis. Caffeine or placebo was administered at 09.00 h, 90 min after the third dose of fluvoxamine (or placebo).

On the morning of each caffeine (or placebo) treatment, after ingesting a light breakfast with no caffeine-containing food or beverages and no grapefruit juice, subjects arrived at the Clinical Psychopharmacology Research Unit at approximately 07.30 h Subjects fasted until 12 noon, after which time they resumed a normal diet (without grapefruit juice or caffeine-containing food and beverages). The single dose of caffeine or placebo was given at 09.00 h. A 7-mL venous blood sample was drawn from an indwelling cannula or by separate venipuncture into a heparinized tube prior to dosage and at the following postdosage times: 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, and 24 h. Samples were centrifuged and the plasma separated and frozen until the time of assay.

The pharmacodynamic effects of caffeine were assessed using a number of tests. The electroencephalogram (EEG) has been extensively used as an objective index of central benzodiazepine-induced sedation [15–18]. At two predose times and during 8 h postdosage at times corresponding to blood sampling, the EEG was measured and digitized over the power spectrum from 4.0 to 31.75 cycles per second (Hz), then fast-Fourier transformed to determine amplitude over the 13.0–31.75 Hz ('beta') band. Subjects' self-ratings of sedative effects and mood state were obtained from a series

of 100-mm visual analogue scales. Ratings of sedation were also performed by trained observers, using the same rating instrument and without knowledge of the treatment condition. Self-ratings and observer ratings and the Digit Symbol Substitution Test (DSST), a 2-min test of psychomotor performance, were administered twice prior to caffeine (or placebo) dosing and at times corresponding to blood sampling [15–18].

Drug and metabolite analysis

Plasma concentrations of caffeine and metabolites were determined by HPLC [19, 20]. The calibration range was 0.1–10 μg mL^{-1}, and within- and between day coefficients of variation (CVs) did not exceed 9%.

Plasma fluvoxamine concentrations were determined by HPLC. After addition of 100 ng of fluoxetine as internal standard, along with calibration samples containing varying known amounts of fluvoxamine (10–500 ng/mL), plasma samples, were alkalinized with 0.1 mL of 1 N NaOH, then extracted with hexane : isobutanol (98.5 : 1.5) using a vortex mixer. The organic extracts were separated, evaporated to dryness, reconstituted with 0.15 mL of mobile phase, and transferred to HPLC autosampling vial [5]. An aliquot of 40 μL was injected onto the HPLC. The instrumentation (Waters Associates, Milford, MA) consisted of a solvent delivery system (flow rate: 1.7 mL min^{-1}), autosampler, and ultraviolet detector operated at 254 nm. The mobile phase was 70% 0.05 M potassium dihydrogen phosphate buffer (pH 3.0) and 30% acetonitrile. The column was a reverse phase C-18 micro-Bondapak (30 cm in length, 3.9 mm in internal diameter). Under these conditions, the retention time of fluvoxamine was approximately 18 min, and that of the internal standard 31 min.

Calibration curves (peak height ratio *vs.* fluvoxamine concentration) were linear ($r^2 > 0.98$) and intercepts did not differ significantly from zero. The limit of sensitivity of the assay was 10 ng mL^{-1}, which was the lowest point on the calibration curve. At 20 ng mL^{-1}, the within-day CV was 8.7%, and 10.9% at 100 ng mL^{-1}. The between-day CVs at 20 and 100 ng mL^{-1} were 14 and 15.5%, respectively.

The caffeine and fluvoxamine analytic procedures did not interfere with each other.

Analysis of pharmacokinetic and pharmacodynamic data

The slope (beta) of the terminal log-linear phase of each caffeine plasma concentration *vs.* time curve was determined by linear regression analysis, and used to calculate the apparent elimination half-life. Area under the plasma concentration curve (AUC) from time zero until the last detectable concentration was determined by the linear trapezoidal method and extrapolated to infinity. In some instances, predose plasma concentrations of caffeine and metabolites were nondetectable, in which case the AUC was corrected for the value at time zero. Apparent oral clearance was calculated as the administered dose of caffeine divided by the total AUC, and the apparent volume of distribution was calculated as clearance divided by beta. The area under the 24-h plasma concentration curve for each of the metabolites was also determined.

For each EEG recording session, the relative beta amplitudes (beta divided by total, expressed as a percentage) were calculated, and the mean of the values from the left and right frontotemporal leads was taken. The mean values from the predose recordings were used as baseline, and all postdosage data were expressed as the increment or decrement over that mean predose baseline value. For self-ratings and observer ratings on visual analogue scales, the mean of the two predose baseline ratings was taken, and postdosage scores were expressed as the increment or decrement relative to this value. Scores on the DSST were analysed similarly.

For each pharmacodynamic variable, the area under the 8-h plot of effect change score *vs.* time was calculated to obtain a single integrated measure of pharmacodynamic action [15–18].

Statistical procedures for pharmacokinetic parameter comparisons included linear regression and Student's *t*-test. Due to the small size and heterogeneous variance in pharmacodynamic data, differences between treatments were analysed using rank-transformed values.

In vitro-in vivo scaling

A previous study determined the effect of fluvoxamine on the biotransformation of caffeine *in vitro* using human liver microsomes [7]. The mean inhibition constant (K_i) for fluvoxamine was 0.08 μM (35 ng mL^{-1}). This value was used to predict the magnitude of the caffeine–fluvoxamine pharmacokinetic interaction *in vivo*, which was then compared with the predicted *in vitro* data [21–26]. If the concentration of caffeine is below the Michaelis-Menten constant (K_m), the ratio of the *in vitro* reaction velocity with (V_I) and without (V_O) coaddition of fluvoxamine, can be approximated as

$$V_I/V_O = K_i([I] + K_i), \quad (1)$$

where [I] is the concentration of fluvoxamine. *In vivo*, the mean ratio of the AUC caffeine when given alone (AUC_O), divided by AUC with coadministration of fluvoxamine (AUC_I) was 0.08. This is numerically equivalent to the ratio of clearance with (CL_I) and without

(CL_O) fluvoxamine. The core assumption of *in vitro-in vivo* scaling is that AUC_O/AUC_I (or CL_I/CL_O) *in vivo* is equal to V_I/V_O *in vitro*. Substituting into equation 1 yields the following:

$$CL_I/CL_O = K_i/([I] + K_i). \quad (2)$$

Actual and predicted values of CL_I/CL_O were compared using available values of plasma concentrations of fluvoxamine [I], with K_i set at 0.08 μM.

Results

Pharmacokinetics

Plasma caffeine concentrations after coadministration of placebo or fluvoxamine are shown in Figure 1. Caffeine concentrations in predose (–0.5 h) plasma samples were between 0 and 3.62 μg mL^{-1}, with mean values of 0.12 μg/mL and 1.41 μg mL^{-1} during Treatment B and Treatment D, respectively.

Coadministration of fluvoxamine with caffeine produced a significant increase in peak plasma caffeine concentration (C_{max}), a prolongation of elimination half-life, an increase in total AUC, and a decrease in apparent oral clearance (Table 1, Figure 1). Caffeine clearance

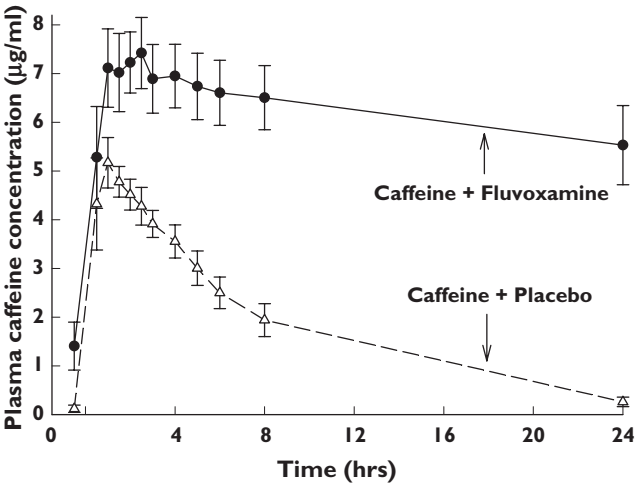

Figure 1
Plasma caffeine concentrations after the administration of caffeine with placebo (Treatment B) or during coadministration with fluvoxamine (Treatment D); each point is the mean (±SEM) for all subjects (n = 7) at the time shown

Table 1
Effect of fluvoxamine on the pharmacokinetics for caffeine and its metabolites

Kinetic variable	Mean (± SEM, n = 7) Value B: Placebo + caffeine*	D: Fluvoxamine + caffeine*	Student's t (P-value)†	Mean difference (with 95% CI)
Caffeine				
C_{max} (μg mL^{-1})	5.81 (0.49)	8.14 (0.75)	–2.47 (<0.05)	–2.33 (–4.64 to –0.02)
t_{max} (h after dose)	1.14 (0.26)	4.57 (3.25)	–1.05 (NS)	–3.43 (–11.42 to 4.56)
$t_{1/2}$ (h)	4.9 (0.65)	55.9 (10.7)	–4.96 (<0.01)	–51.0 (–76.1 to –25.8)
AUC (μg mL^{-1} h^{-1})	46.3 (7.0)	635 (146)	2.45 (<0.01)	–589 (–940 to –238)
Volume of distribution				
L	40.0 (2.5)	44.7 (8.50)	–0.48 (NS)	4.7 (–6.0 to 16.3)
L kg^{-1}	0.50 (0.04)	0.54 (0.10)	–0.38 (NS)	0.04 (–0.07 to 0.21)
Clearance				
mL min^{-1}	105 (17.6)	9.12 (2.02)	4.66 (<0.01)	95.7 (54.9 to 135.6)
mL min^{-1} kg^{-1}	1.34 (0.24)	0.14 (0.03)	4.77 (<0.01)	1.19 (0.67 to 1.72)
Paraxanthine				
24-h AUC (μg mL^{-1} h^{-1})	27.3 (3.09)	9.03 (1.82)	4.70 (<0.01)	18.3 (8.7 to 27.7)
Theobromine				
24-h AUC (μg mL^{-1} h^{-1})	14.8 (3.37)	18.15 (4.92)	–0.59 (NS)	–3.4 (–17.2 to 10.5)
Theophylline				
24-h AUC (μg mL^{-1} h^{-1})	1.96 (0.94)	5.07 (1.14)	–2.19 (P = 0.07)	–3.1 (–6.5 to 0.4)

**Oral dose of caffeine = 250 mg; C_{max}, peak plasma concentration; t_{max}, time to reach C_{max}; $t_{1/2}$, elimination half-life; AUC, area under the concentration vs. time curve; NS, not significant; CI = confidence interval; †Student's t-test evaluated differences between Treatments B and D.*

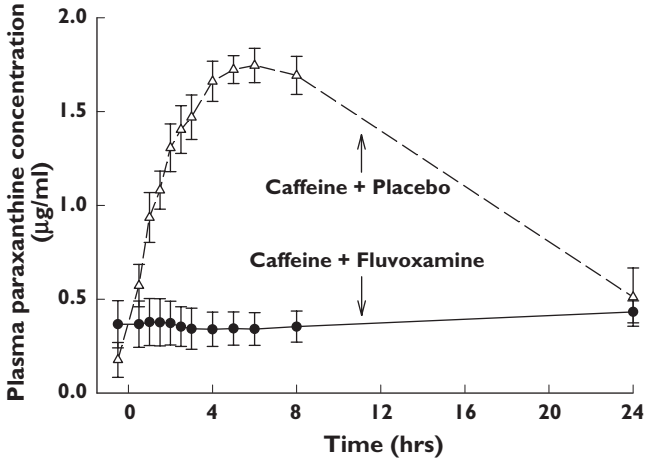

Figure 2
Plasma paraxanthine concentrations after the administration of caffeine with placebo (Treatment B) or during coadministration with fluvoxamine (Treatment D); each point is the mean (±SEM) for all subjects (n = 7) at the time shown

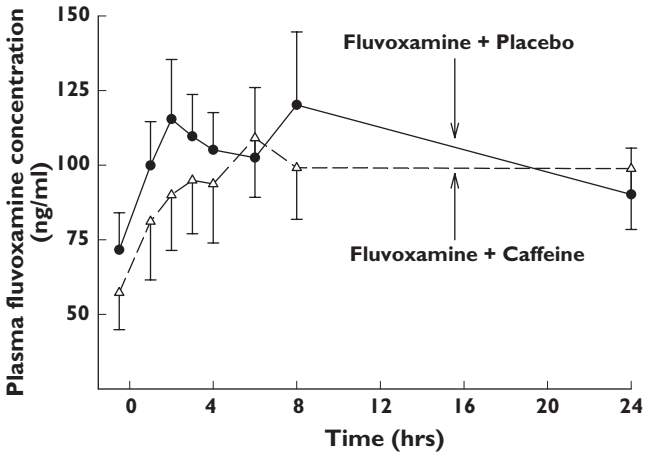

Figure 3
Plasma fluvoxamine concentrations after the administration of fluvoxamine with placebo (Treatment C) or during coadministration with caffeine (Treatment D); each point is the mean (±SEM) for all subjects (n = 7) at the time shown

Table 2
Values of 8-h pharmacodynamic effect area data for the four treatment conditions

Pharmacodynamic effect†	Mean (±ISEM, n = 7) 8-h Effect Area* A: Placebo + Placebo	B: Placebo + Caffeine	C: Fluvoxamine + Placebo	D: Fluvoxamine + Caffeine
Observed-rated sedation	22.4 (12.8)	7.5 (5.0)	12.5 (6.1)	7.4 (5.1)
Self-rated sedation	–6.82 (12.2)	–75.5‡ (36.7)	–1.7 (24.0)	–55.1 (25.0)
Digit Symbol Substitution Test	–6.1 (9.2)	32.0‡ (9.7)	15.9 (12.8)	16.3 (11.7)
Beta EEG amplitude (%)	4.4 (3.7)	0.2 (9.2)	19.3 (2.5)	11.3 (8.7)

**Effect areas were calculated from change scores (vs. baseline) using the trapezoidal method; † For sedation, higher numbers indicate higher sedation ratings; ‡P < 0.05 compared with Treatment A.*

during fluvoxamine cotreatment was less than 10% of control values (Treatment B *vs.* Treatment D). The 24-h AUC of paraxanthine also decreased significantly after coadministration of fluvoxamine (Figure 2).

Mean plasma fluvoxamine concentrations were consistent with the fluvoxamine dosing schedule, and did not significantly differ between the two trials (Figure 3). The mean (±SEM) AUC_{0-8} for fluvoxamine was 886 (±139) ng mL^{-1} h^{-1} during the caffeine placebo (Treatment C) compared with 787 (±144) ng mL^{-1} h^{-1} for fluvoxamine during the caffeine treatment phase (Treatment D). This difference was not significant (mean difference: 99 ng mL^{-1} h^{-1}; 95% CI: −102 to 301).

Pharmacodynamics

Administration of caffeine alone (Treatment B) produced a decrease in self-rated sedation, improved psychomotor performance (the DSST), and small changes in observer-rated sedation and beta amplitude on the EGG compared with double-placebo treatment (Treatment A, Table 2). Administration of fluvoxamine alone (Treatment C) did not increase sedation (either self- or observer-rated) relative to placebo treatment (Treatment A). Coadministration of caffeine with fluvoxamine (Treatment D) did not produce any significant changes in pharmacodynamics compared with placebo with caffeine (Treatment B). Based on self-ratings of sedation,

none of the subjects were more alert after caffeine and fluvoxamine (Treatment D) compared with caffeine alone (Treatment B). All but three subjects were more alert according to observer-ratings for sedation with caffeine alone (Treatment B); the increase in sedation with caffeine-fluvoxamine administration (Treatment D) in these three subjects was less than 10%. With the exception of one subject, EEG beta amplitude increased with caffeine-fluvoxamine treatment (Treatment D) compared with caffeine alone (Treatment B), indicating that fluvoxamine did not enhance alertness associated with caffeine.

None of the subjects experienced clinically important adverse reactions during the caffeine-fluvoxamine coadministration trial (Treatment D).

In vitro-in vivo scaling

The minimum and maximum plasma fluvoxamine concentrations averaged 55 ng mL^{-1} (127 nM) and 109 ng mL^{-1} (251 nM), respectively, when the drug was given with caffeine. Using these values in equation 2, predicted caffeine CL_I/CL_O ratios of 0.39 and 0.26, respectively both of these ratios are larger than the actual mean ratio of 0.08. Therefore, the use of plasma fluvoxamine concentrations in the scaling model greatly underestimates the extent of the *in vivo* interaction. Entering a CL_I/CL_O ratio of 0.08 into equation 2 yields an apparent enzyme-available fluvoxamine concentration of 800 nM, corresponding to a value approximately 6.3 times higher than the observed minimum plasma fluvoxamine concentration.

Discussion

Fluvoxamine (four doses of 100 mg over 2 days) produced a large and highly significant prolongation of elimination half-life and impairment of oral clearance of caffeine, a CYP1A2 substrate [7]. Estimation of pharmacokinetic parameters in our study had limitations in that the duration of sampling was only 24 h after single caffeine doses. Nonetheless, the findings are consistent with previous reports [8, 12], and with *in vitro* data demonstrating that fluvoxamine is a potent inhibitor of caffeine biotransformation [7, 10] and of other CYP1A2-mediated reactions [9, 26]. Utilizing a previously reported K_i value for fluvoxamine inhibition of caffeine biotransformation [7] and measured plasma fluvoxamine concentrations, we determined the extent to which *in vitro* findings were consistent with the clinical fluvoxamine–caffeine pharmacokinetic interactions. Plasma fluvoxamine concentrations predicted an interaction that was substantially less than that observed. Tissue distribution studies have demonstrated that concentrations of lipophilic drugs (such as fluvoxamine) in the liver may greatly exceed those in blood or plasma [23, 25, 27–31]. Therefore, plasma fluvoxamine concentrations may be considerably lower than those at the actual site of metabolic inhibition, explaining why the *in vitro-in vivo* scaling procedure underpredicts the observed clinical pharmacokinetic interaction in the present study and in previous reports [32].

Subjects were asked to abstain from all caffeine-containing foods and beverages for 24 h prior to each study phase. Despite such advice, predose plasma samples from nearly all subjects contained measurable concentrations of caffeine and paraxanthine. In agreement with this finding, a previous study demonstrated that self-reports of caffeine consumption typically do not accurately reflect acute exposure [33].

The increased plasma caffeine concentrations during coadministration with fluvoxamine were not accompanied by enhanced pharmacodynamic activity of caffeine. Several alerting actions of caffeine were observed using tests for mood, sedation, psychomotor performance and EEG, but none were augmented by coadministration of fluvoxamine. The lack of a significant caffeine–fluvoxamine pharmacodynamic interaction might be the result of a number of factors. The subjects who participated in this study, four out of seven of whom consumed caffeine-containing beverages on a regular basis, may have been tolerant to the stimulating effects of higher concentrations of caffeine, even though caffeine alone caused significant improvement in psychomotor performance and decreases in self-rated sedation compared with double-placebo administration. Caffeine doses in excess of 5 mg kg^{-1} are reportedly required to produce clinically important effects such as mild anxiety, respiratory stimulation, and cardiovascular actions [34]. Caffeine doses in the present study (250 mg, approximately 3.5 mg kg^{-1}) may not have been sufficient to produce adverse effects even after augmentation by fluvoxamine. However, the findings from this single-dose caffeine study predict extensive caffeine accumulation with daily caffeine ingestion and fluvoxamine treatment. Based upon our single dose caffeine data, simulated plasma caffeine concentrations once-daily caffeine ingestion (250 mg) and fluvoxamine treatment over 7 days (Figure 4) are predicted to reach a range that might produce untoward CNS effects [13]. Caffeine accumulation could be further augmented with the consumption of caffeine repeatedly throughout a 24-h period.

The findings from this study demonstrate a substantial pharmacokinetic interaction between caffeine and fluvoxamine in the absence of a pharmacodynamic

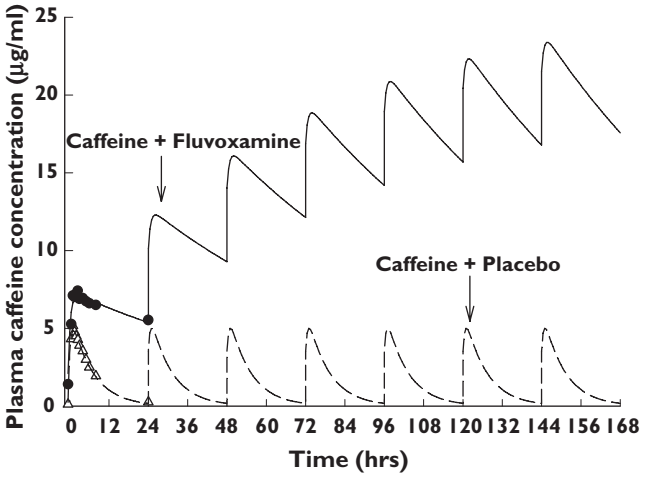

Figure 4
Simulated plasma concentrations of caffeine after coadministration with either fluvoxamine or placebo for 7 consecutive days. It is assumed that the dose of caffeine and fluvoxamine are the same for each 24-h interval. Actual mean data points from the pharmacokinetic study are shown

interaction when caffeine is given as a single dose. Extended or repeated caffeine consumption and fluvoxamine treatment is likely to cause substantial caffeine accumulation and the possibility of a clinically important pharmacodynamic interaction.

Supported in part by grants MH-58435, DA-05258, DA-13209, DA-13834, DK-58496, DA-05258, AG-17880, AT-01381, and RA-00054 from the Department of Health and Human Services.

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